

Quantitative Evaluation of the Radon and Lung Cancer Association in a Case Control Study of Chinese Tin Miners¹

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ABSTRACT

Studies of underground miners have consistently shown an increased risk of lung cancer with cumulative exposure to radon-222 and its decay products. Although the deleterious effects of high radon exposure are clear, questions regarding the shape of the exposure-response relationship, and the effects of time factors such as attained age, time since exposure and early age at first exposure, the effect of exposure rate, and the joint association of radon exposure and tobacco use have not yet been fully clarified. This report considers these questions by fitting various models for the relative odds of disease to 74 male lung cancer cases who were diagnosed between 1981 and 1984 and were alive in 1985 and an equal number of controls. All subjects are current or past employees of the Yunnan Tin Corporation, Gejiu City, China, who reside in the local area. Workers were interviewed to obtain information on work history, from which radon exposure in cumulative working level months and arsenic exposure were estimated, and on tobacco use.

Results indicate that excess relative risk increases by 1.7% per cumulative working level month [95% confidence interval (0.5, 5.4)]. The linear exposure response relationship significantly declines with year since last radon exposure ($P = 0.02$). The risk trend also declines with increasing exposure rate ($P = 0.001$), indicating that long duration of exposure at a low rate may be more deleterious than short duration of exposure at a high rate. A unique aspect of this study population is the very early ages at first radon exposure for many of the workers, about 37% of the radon-exposed workers were first exposed under the age of 17 years. The analysis shows no modification of the radon lung cancer relationship with age at first exposure. These patterns of risk with radon exposure are generally consistent with those reported in the recent National Academy of Sciences' Biological Effects of Ionizing Radiations IV report.

The primary method of tobacco consumption in this area of China is by waterpipe. Lung cancer risk increases with pipe-years of use. The joint analysis of tobacco use and radon exposure supports the Biological Effects of Ionizing Radiations IV conclusion that the most likely model is between additive and multiplicative.

The variations of the radon lung cancer relationship by years since last exposure and exposure rate are not affected by adjustment for arsenic exposure.

INTRODUCTION

Studies of underground miners show that the risk of lung cancer increases with exposure to radon and its short-lived decay products, and that the increase in risk is linear over a broad range of cumulative exposure (1-14). Although the deleterious effects of high radon exposure are clear, questions regarding the shape of the exposure-response relationship, the effects of attained age, time since exposure and early age at first exposure, the effect of exposure rate, and the joint association

of radon exposure and tobacco use have not yet been fully clarified. In the public health arena, there is currently intense interest in the effects of exposure to radon, since radon gas, a natural decay product of the radium and uranium in soils, has been found to accumulate in homes. Exposure rates in some homes have been found which over a lifetime can expose residents to cumulative levels which are as high or higher than are received by miners. The only sources of data currently available to quantitatively assess risk due to home radon exposure are studies of underground mines.

The National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiations (the BEIR IV Committee) combined data from four major cohort studies of miners and carried out the most comprehensive analysis to date. They found a linear increase in the relative risk of lung cancer due to radon exposure which was modified by various factors (15). They found that the gradient of risk declines with attained age and with time since exposure occurred. There was no consistent effect with age at first exposure, although data were limited, since miners generally start employment in their mid-twenties. The effect of duration or rate of exposure, after accounting for cumulative exposure, was mixed, increasing with increasing duration (or decreasing rate) in some data sets, but not in others. However, the BEIR IV joint risk analysis must be viewed as tentative, as the analysis was based on a total of only 360 lung cancer cases. Thus, independent verification of their results in other data sets is important.

Tobacco use is the most important cause of lung cancer. Of major scientific and public health interest is the form of the relative risk function with combined exposure to radon and tobacco smoke. Data are currently very limited for modeling the relative risk for joint exposure, but are generally consistent with a multiplicative relationship (2, 15-21). Since the multiplicative relationship is consistent with available data, it has generally been the model of choice for projection of lifetime risks (15, 20, 22-25). However, a wide range of models from supraadditive to supramultiplicative are also plausible (15). The additive model has less support and has been rejected statistically in formal analyses of the largest data set available (15, 17, 18, 21).

Qiao *et al.* (26) recently reported on a case control study among male employees of the YTC,³ Yunnan Province, China, involving 107 prevalent lung cancer cases, who were diagnosed between 1971 and 1984 and who were alive at time of interview in 1985. We use the 74 cases who were diagnosed within 4 years of interview and present a quantitative assessment of patterns of lung cancer risk due to radon exposure and due to radon exposure and tobacco use. These data constitute the second largest case series of its type for studying radon and tobacco use.

³ The abbreviations used are: YTC, Yunnan Tin Corporation; CWLM, cumulative working level month.

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MATERIALS AND METHODS

Details of the design of this study are presented elsewhere (26). Briefly, Gejiu City, Yunnan Province has the highest rate of lung cancer among males in China and the YTC is its largest employer. The YTC operates tin mines, ore dressing plants, smelters, and related operations and has approximately 33,000 male and 11,000 female workers, active and retired. Among this group of workers, about 90 lung cancer cases per year (mostly males) are reported to the Cancer Registry of the Labor Protection Institute, a department of the YTC. The YTC considers lung cancer an occupational disease and accordingly compensates the patient and family. Therefore, it is felt that registry files are substantially complete. The current study group includes all male lung cancer cases between ages 35 and 80 years who are or were employed by the YTC, who were reported to the Cancer Registry, and who were alive at the time of interview. All cases were confirmed by an independent panel of pathologists, clinicians, and cytologists. To reduce travel burden for the interviewers, cases were restricted to those who reside in the local area. To minimize any distorting effects of prevalent cases, we restrict the case group to the 74 cases diagnosed from 1981.

A control who resided in the local area was selected for each case from YTC worker lists of current and retired male employees and age-matched within 5-year age groups. Exposures of each control were adjusted to reflect values at the time of case diagnosis (with adjustment for any lag interval, if appropriate). Mean age of cases and of controls was 62 years.

Based on personal interviews, detailed data were obtained on tobacco use and on lifetime work history, including job title, work site and starting/stopping dates. Although estimates of cumulative radon exposure reflect only YTC mine experience, few workers had non-YTC, occupational radon exposure.

Estimates of radon and radon progeny were obtained for each work area within each mine or factory unit and within three eras (≤ 1952 , 1953–1972, ≥ 1973). The year 1953 was selected to demarcate an era, since major operational (large scale tunnel production) and administrative changes occurred around this time which substantially impacted the work situation. Estimates for years before 1953 were obtained from 117 samples taken contemporaneously by recreating primitive mine conditions in 13 local small mine pits that were in operation before 1949 (27).

Estimates of radon levels between 1953 and 1972 were obtained from 413 measurements obtained by recreating conditions in tunnels and galleries in original areas or by measuring areas in nearby mines which are operated by local communes using comparable mining techniques and which have similar configurations.

Measurement of radon and radon progeny began in earnest in 1973. Estimates of exposure after 1972 were based on over 26,000 area measurements of radon and radon progeny levels. Industrial hygienists with assistance from older workers made adjustments to account for unmeasured areas. For the years after 1972, adjustments were also made for job title. Exposure for workers who were only intermittently underground were reduced accordingly.

For each underground worker, exposure to radon was estimated in units of cumulative working level months. One Working Level equals any combination of radon daughters in one liter of air which results in the ultimate emission of 130,000 MeV of energy from alpha particles. CWLM is a time-integrated exposure and is the product of time, in units of working months which is taken to be 170 h, and working levels. Estimated exposure rates have dropped only in the most recent era. Median values for the years before 1953, 1953–1972, and 1973–1980 are 1.64, 1.94, and 0.77 Working Levels, respectively. Estimated cumulative radon exposure ranged from 0 to 1680 CWLM, with means for cases and controls of 507 and 247, respectively.

In 1963, each mine of the YTC established a department concerned with ventilation practices. Some improvements were made during the late 1960s, however, major, large scale changes were not initiated until 1972.⁴

In 1977 and 1978 the Labor Protection Institute also assessed radon equilibrium levels for the various mines. In the small pit operations,

equilibrium levels ranged from 20 to 84% with a mean of 72%. In the larger tunnels, the equilibrium levels had a mean of about 62%.

Exposure to arsenic was based on airborne dust concentrations, which have been extensively measured since the 1950s. As with radon, a cumulative arsenic exposure index was computed for each YTC employee. A separate report on the effects of arsenic exposure has been published (28). In this report, we consider arsenic only in the context of its impact on radon risk.

We analyze data using standard regression procedures for matched case control studies, although we replace the usual exponential relative risk with alternative functions (29, 30). The various forms of the relative risk, R , are detailed in the next section.

RESULTS

Let w denote CWLM exposure up to 5 years prior to time of diagnosis for the case and for its matched control. Epidemiological studies of human populations (1–14) and experimental animal studies (15) suggest a linear relationship between cumulative radon exposure and lung cancer. Table 1 and Fig. 1 show that relative risks rise with increasing CWLM exposure. The category-specific relative risks are the standard estimates for pairwise matched data and are obtained under the model

$$R(w) = 1 + \theta_i \quad (A)$$

where w is in the i th exposure category and θ_i is the unknown excess relative risk parameter.

The category-specific relative risk, $1 + \theta_i$, can be compared to a linear relative risk model for the continuous exposure w , namely,

$$R(w) = 1 + \beta w \quad (B)$$

The estimated value for β is 0.017. [For the actual fittings, we replaced β by its exponential $\exp(\beta)$.] The estimated linear

Table 1 Numbers of lung cancer cases and controls and matched relative risk estimates by categories of cumulative radon exposure, as measured by cumulative working level months

	CWLM						Total
	0	1–99	100–199	200–399	400–799	≥ 800	
Cases	5	4	8	22	16	19	74
Controls	32	9	6	10	9	8	74
Mean	0.0	48.4	151.1	272.5	585.9	1097.6	376.7
CWLM							
Relative risk	1.0	1.3	6.4	11.4	7.9	13.2	

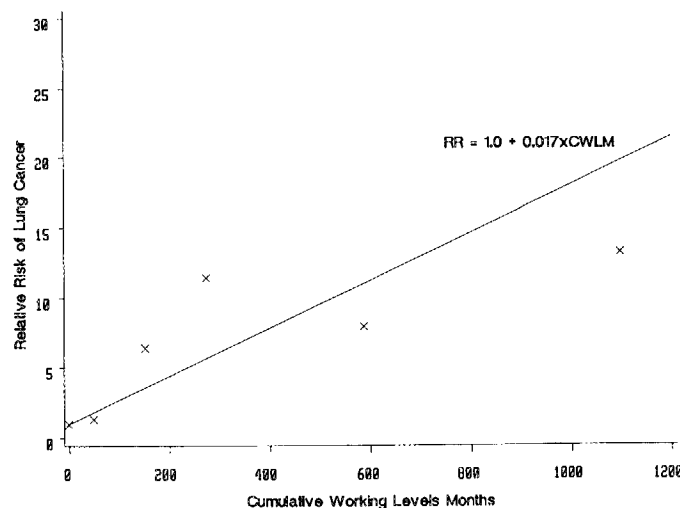


Fig. 1. Matched relative risk of lung cancer within categories of cumulative working level months and the fitted relative risk regression line.

⁴ B-L. Mao, unpublished data, 1977.

relative risk function from model B is shown in Fig. 1 and is seen to fit the category-specific relative risks quite well. For continuous w , deviations from the linear model were evaluated relative to the linear-quadratic model,

$$R(w) = 1 + \beta w + \gamma w^2 \quad (C)$$

and the linear-exponential model,

$$R(w) = (1 + \beta w)\exp(-\gamma w) \quad (D)$$

Neither the first ($P = 0.13$) nor second ($P = 0.43$) of these models provided a significantly better fit than the linear.

We assess whether a categorical variable, x , modifies the linear relationship between CWLM and lung cancer by using the model

$$R[w(x)] = 1 + \beta_j w \quad (E)$$

where β_j is the linear radon effect within the j th category of x . A $J - 1$ degree of freedom likelihood ratio χ^2 test of homogeneity is obtained as the difference in the deviances between models B and E.

The overall estimate of β is 0.017, indicating that excess relative risk increases approximately 1.7% per CWLM [95% CI (0.5%, 5.4%)]. This increase is consistent with values found in studies of other miner populations (15, 16, 20). Based on model E, Table 2 shows that the trend in risk with CWLM exposure generally declines with years since cessation of radon exposure ($P = 0.015$), from 12.3% per CWLM within 5–14 years since last exposure to 0.7% per CWLM after 25 years. In addition, there is a significant decline in the CWLM slope parameter with increasing exposure rate ($P = 0.001$). The decline in the β estimates with rate suggests that long duration exposure at a low rate may be more deleterious than short duration exposure at high radon levels. Mean exposure rates within rate categories are 10.8, 21.3, and 35.8 WLM per year. Data are not sufficient to jointly analyze exposure rate and years since cessation of exposure as modifying factors of the trend in risk with cumulative radon exposure. In these data, 37% of exposed workers started employment under the age of 13 years. Table 2 shows that there is no evidence of a change

Table 2 Lung cancer risk estimates of the effects of CWLM and twice the maximum log-likelihood under linear relative risk models for radon, models B and E

Variable	Cases	Controls	$\beta \times 100$	Deviance	P^a
CWLM	74	74	1.7 ^b	76.2	
Time since last exposure (year)					
0–4 ^c	17	5	3.0	65.8	0.015
5–14	11	4	12.3		
15–24	23	9	6.0		
≥25	18	24	0.7		
Attained age (year)					
35–54	20	16	2.5	74.0	0.34
55–64	31	33	3.3		
≥65	23	25	0.8		
Exposure rate (CWLM/year)					
<15 ^c	26	9	11.3	61.5	0.001
15–29	24	14	1.6		
≥30	19	19	1.3		
Age first exposed (year)					
<13 ^c	25	16	1.2	74.1	0.35
13–18	27	10	2.5		
≥19	17	16	2.9		

^a P value for test of homogeneity.

^b Five cases and 32 controls had no radon exposure.

^c 95% confidence interval (0.5, 5.4).

in radon effects for early age at first radon exposure. There is also a nonsignificant decline in the CWLM trend with age.

Tobacco use is an important determinant of lung cancer. In this area of China, the predominant method of tobacco consumption is by waterpipe. Cigarettes are consumed, but not intensively, as in these data cigarette-only smokers average 12 cigarettes per day, while waterpipe smokers averaged 9 cigarettes per day. Among cigarette-only smokers, waterpipe-only smokers and mixed smokers, the crude odds ratios were 1.2, 3.6, and 3.5, respectively, relative to nonusers of tobacco. For the remainder of the analyses, we use pipe-years, the product of duration of use in years up to 1 year before the diagnosis of the case and quantity of tobacco used in liang (50 g) per month, as the measure of tobacco exposure. In the full study population, Qiao *et al.* found a 2–5-fold increase in risk of lung cancer with greater tobacco consumption among waterpipe users, but again little increase in risk with cigarette use (26).

The joint relationship between pipe smoking and radon exposure is considered in Tables 3–5. Table 3 shows data cross-classified by the two factors. Although data are sparse, crude relative risks increase with increasing pipe-years and with increasing radon exposure.

The relationship between radon exposure and pipe smoking is formally evaluated by defining a model for the joint exposures which incorporate the multiplicative and additive relative risk models as submodels in a wider class of models and carrying

Table 3 Crude relative risks of lung cancer and number of cases and controls by categories of cumulative working level months and pipe-years

Pipe-years	CWLM					Total
	0–99	100–199	200–399	400–799	≥800	
0	1.0	6.0	0.0	0.0	∞	1.0
	2/12 ^a	1/1	0/2	0/1	3/0	6/16
1–114	0.4	3.0	14.0	42.0	12.0	2.1
	1/16	1/2	7/3	7/1	2/1	18/23
115–220	12.0	0.0	14.0	15.0	18.0	3.7
	3/6	0/2	7/3	5/2	6/2	21/15
≥220	2.6	36.0	24.0	4.8	9.6	3.9
	3/7	6/1	8/2	4/5	8/5	29/20
Total	1.0	6.1	10.0	8.1	10.8	
	9/41	8/6	22/10	16/9	19/8	

^a Cases/controls.

Table 4 Results of matched regression analyses of continuous data on cumulative radon exposure (w) and pipe-years of tobacco use (y), with adjustments for radon exposure rate (r) or years since last exposure (c) and for duration of pipe use (d)

Model ^a	Deviance	Number of parameters
A1: $R[w(r), y(d); \hat{\lambda} = 0.6]$	56.4	7
A2: $R[w(r), y(d); \hat{\lambda} = 1.0]$	56.2	6
A3: $R[w(r), y(d); \hat{\lambda} = 0.0]$	57.5	6
B1: $R[w(c), y(d); \hat{\lambda} = 0.0]$	56.3	8
B2: $R[w(c), y(d); \hat{\lambda} = 1.0]$	59.9	7
B3: $R[w(c), y(d); \hat{\lambda} = 0.0]$	56.3	7
C1: $R[w(r), y; \hat{\lambda} = 0.3]$	57.0	5
C2: $R[w(r), y; \hat{\lambda} = 1.0]$	57.4	4
C3: $R[w(r), y; \hat{\lambda} = 0.0]$	57.6	4
D1: $R[w(c), y; \hat{\lambda} = -0.1]$	56.3	6
D2: $R[w(c), y; \hat{\lambda} = 1.0]$	61.3	5
D3: $R[w(c), y; \hat{\lambda} = 0.0]$	56.3	5
E1: $R[w, y(d); \hat{\lambda} = 0.1]$	71.8	5
E2: $R[w, y(d); \hat{\lambda} = 1.0]$	73.6	4
E3: $R[w, y(d); \hat{\lambda} = 0.0]$	71.9	4
F1: $R[w, y; \hat{\lambda} = 0.0]$	72.1	3
F2: $R[w, y; \hat{\lambda} = 1.0]$	74.9	2
F3: $R[w, y; \hat{\lambda} = 0.0]$	72.1	2
G: $R[w]$	76.2	1
H: $R[y]$	93.9	1

^a Relative risk models are defined by Equation F (see "Results"), where x denotes either exposure rate (r) or years since last exposure (c), where β_x and γ_x denote excess relative risk parameters for w and y within categories of the adjusting variable, x or d , respectively, and where λ is a mixing parameter, with $\lambda = 1$ for a multiplicative association and $\lambda = 0$ for an additive association.

Table 5 Results of tests of various hypotheses based on models from Table 5. (See footnote in Table 5 for model definition.)

	χ^2 (dof)	P value
Modification of radon effect by exposure rate		
C1 vs. F1	15.1 (2)	0.001
Modification of radon effect by years since last exposure		
D1 vs. F1	15.8 (3)	0.001
Modification of pipe-years effect by duration of pipe use		
A1 vs. C1	0.6 (2)	0.74
B1 vs. D1	0.0 (2)	0.90
E1 vs. F1	0.3 (2)	0.86
Multiplicative relationship for w and y		
C2 vs. C1 ^a	0.8 (1)	0.37
D2 vs. D1 ^b	5.0 (1)	0.02
Additive relationship for w and y		
C3 vs. C1 ^a	0.6 (1)	0.44
De vs. D1 ^b	0.0 (1)	0.89
Radon as a risk factor		
H vs. F2	19.0 (1)	<0.001
H vs. F3	21.8 (1)	<0.001
Pipe-years as a risk factor		
G vs. F2	1.3 (1)	0.25
G vs. F3	4.1 (1)	0.04

^a Cumulative radon exposure effects adjusted for exposure rate.^b Cumulative radon exposure effects adjusted for years since last radon exposure.

out tests of hypotheses relative to the larger model.

The capability of analyzing various models using the categorizations of Table 3 for the variables is limited by the sparseness of the data and by an inability to adjust for other important factors. This limitation can be partially offset by using continuous variables for radon exposure and pipe use. Suppose w and y denote CWLM and pipe-years of exposure. Fig. 1 indicates that the marginal data in CWLM is well fit by a linear function. Although less definitive, similar analyses suggest that a linear function is also appropriate for pipe-years. Table 4 shows results of model fittings with w and y continuous, while adjusting for categories of radon exposure rate (r) or time since last exposure (c) and for categories of duration of pipe use (d). Table 5 shows related tests of hypotheses. Specifically, the relative risk is defined as a combination of a multiplicative and an additive model, namely,

$$R[w(x), y(d); \lambda] = [(1 + \beta_x w)(1 + \gamma_d y)]^\lambda [1 + \beta_x w + \gamma_d y]^{1-\lambda} \quad (F)$$

where x represents exposure rate (r) or time since last exposure (c), where β_x and γ_d denote trend parameters for cumulative radon exposure and cumulative pipe-years exposure within categories of x and d , and where λ is an indexing parameter. At $\lambda = 1$, R defines a multiplicative association between w and y , and at $\lambda = 0$, R defines an additive association. The λ is an unknown parameter which describes a smooth deformation of the relative risk function from subadditive ($\lambda < 0$) through supramultiplicative ($\lambda > 1$). The categories for r and c are defined in Table 2 and the categories of duration of pipe use are 0, <30, 30–39, and ≥ 40 years. $R[w, y; \lambda]$ denotes the model where β and γ do not depend on categories of another variable.

Table 5 shows that pipe-years is a significant risk factor, and that adjusting for duration of pipe use does not improve the fit. Table 5 also shows that the modification in the CWLM effect with exposure rate and time since cessation of exposure seen in Table 2 persists after adjustment for tobacco use, for example,

model A1 versus E1 and model B1 versus E1. For model F2, the overall estimate of β , adjusted for pipe-years, is 1.4% [95% C1 (0.4%, 4.8%)]. For model C2, estimates of the β values within categories of exposure rate are 12.0, 1.6, and 0.7%, and for model D2 the estimates within categories of years since last exposure are 2.5, 18.0, 5.5, and 0.3%. These are similar to the estimates in Table 2. For the additive model F3, the overall estimate of β is 4.3% (95% C1 [0.4%, 43.4%]). Using C3, the β values within rate categories are 33.2, 4.7, and 2.5% and using D3, the β values within cessation categories are 18.7, 81.5, 34.4, and 0.2%.

Although λ is estimated with great uncertainty, the maximum likelihood estimate of λ under model F is 0.3 when radon exposure is adjusted for intensity and -0.1 when adjusted for cessation. The deviances are very similar. Table 5 shows that a multiplicative model for the joint radon and pipe-years exposure is consistent with the data when cumulative radon exposure is adjusted for exposure rate, but is rejected if radon is adjusted for cessation. The additive model is consistent with the data with either adjustment factor.

Finally, underground miners are exposed to radon gas and to mine dusts which contain arsenic (and other potential carcinogens), while surface workers are not exposed to radon but are exposed to arsenic-containing dusts during ore dressing and smelting operations. Two cases and 28 controls were not exposed to arsenic or radon, while three cases and four controls were exposed to arsenic but not to radon. Exposure to arsenic is defined as a time-weighted average, the product of concentration in mg/m³ and duration of exposure in months. The ability to disentangle risks from the separate exposures is limited, because most subjects are exposed to both agents. Table 6 shows crude relative risks for a cross-classification of arsenic and radon exposures. Risks are seen to rise with increasing cumulative exposure to each agent.

We fit a model similar to expression F with pipe-years replaced by the index of cumulative arsenic exposure, namely,

$$R[w(x), a; \lambda] = [(1 + \beta_x w)(1 + \gamma_a a)]^\lambda [1 + \beta_x w + \gamma_a a]^{1-\lambda} \quad (G)$$

where a denotes cumulative arsenic exposure, and x denotes effects of categories of other variables. Cumulative arsenic exposure is modeled only as a continuous exposure, as there are insufficient data to consider the effects of years since last arsenic exposure, age, arsenic exposure rate, and age at first arsenic exposure jointly with the similar variables for radon exposure.

Because of the limited data and the high correlation between exposures, there is no preferred model for adjusting radon effects for arsenic exposure. Table 7 shows the radon exposure

Table 6 Numbers of cases and controls and crude odds ratios for lung cancer by cumulative working level months and cumulative arsenic exposure

As exposure ^a	CWLM						Total
	0	1–99	100–199	200–399	400–799	800–1680	
0	1.0 2/28 ^b						1.0 2/28
0.1–27.9	7.0 1/2	3.1 2/9	7.0 2/4	21.0 9/6	28.0 2/1	28.0 2/1	11.0 18/23
28.0–67.9	28.0 2/1	∞ 1/0	14.0 2/2	98.0 7/1	16.8 6/5	49.0 7/2	31.8 25/11
68.0–256.0	∞ 0/1	∞ 1/0	∞ 4/0	28.0 6/3	37.3 8/3	28.0 10/5	33.8 29/12
Total	1.0 5/32	2.8 4/9	8.5 8/6	14.1 22/10	11.4 16/9	15.2 19/8	

^a Time-weighted average exposure, mg/m³ \times months exposed. Exposure categorized by quartiles.^b Cases/controls.

Table 7 Lung cancer risk estimates of the effects of CWLM and twice the maximum log-likelihood under linear relative risk models for radon, model G, with multiplicative ($\lambda = 1$) and additive ($\lambda = 0$) adjustment for cumulative arsenic exposure

Variable	Multiplicative model			Additive model			Max likelihood fit		
	$\beta \times 100$	Deviance	Prob ^a	$\beta \times 100$	Deviance	Prob ^a	$\hat{\lambda}$	Deviance	Prob ^a
CWLM	0.03 ^b	72.5		2.3 ^b	66.9		-0.4	64.9	
Time since last exposure (year)									
0-4	0.1	64.0	0.04	5.9	59.6	0.06	0.3	58.2	0.08
5-14	0.8			11.9					
15-24	0.2			2.4					
≥ 25	0.0			0.0					
Attained age (year)									
35-54	0.4	68.8	0.16	2.3	65.0	0.39	0.0	65.0	0.95
55-64	0.4			4.9					
≥ 65	0.0			0.0					
Exposure rate (CWLM/year)									
<15	5.6	57.3	0.001	17.4	57.0	0.008	0.2	57.1	0.02
15-29	0.4			2.3					
≥ 30	0.2		1.4						
Age first exposed (years)									
<13	0.1	68.4	0.13	1.3	64.1	0.25	-0.3	63.4	0.47
13-18	0.2			2.2					
≥ 19	1.0		6.1						

^a P value for test of homogeneity.^b 95% confidence interval, (0.0, 8.7) with multiplicative adjustment for arsenic and (0.3, 17.1) with additive adjustment for arsenic.

effects for categories of several variables, as in Table 2, with a multiplicative adjustment for arsenic ($\lambda = 1$) and with an additive adjustment ($\lambda = 0$). The maximum likelihood estimate of the mixing parameter $\hat{\lambda}$, is also given. The patterns of effect modification to the β parameter are similar to those of Table 2, a decline with years since last exposure and exposure rate. There is a nonsignificant decline in risk with attained age. The joint association of radon and arsenic is likely between multiplicative and additive.

Although not shown, the results in Table 7 are essentially unchanged when model G is augmented by a multiplicative pipe-years effect. However, insufficient data preclude more detailed analysis of joint exposure to radon, arsenic, and tobacco smoke.

DISCUSSION

We found that the excess relative risk of lung cancer increases at a rate of approximately 1.7% per CWLM. Other researchers have found similar increases. The BEIR IV report variously estimated the excess as 1.3% or 1.5% per CWLM (15), while in a survey of eight studies Lubin estimated an excess of 1.5% per CWLM (16). Thomas *et al.* estimated a similar 2.3% per CWLM (21). The estimates of the excess relative risk pattern in the individual cohorts ranged from 0.5 to 3.0% per CWLM. These estimates, however, are statistically homogeneous, and the observed variation is no more than expected by chance (15, 16).

The BEIR IV analysis was based on a joint analysis of four cohorts of radon-exposed miners. The estimate of the linear exposure disease relationship declined with time since exposure. Exposure more than 15 years prior to attained age produced half the effect on the excess relative risk as exposures 5-15 years prior. Exposure within 5 years was assumed unrelated to lung cancer occurrence. Because of limited data, we instead used the variable years since last worked underground to evaluate whether excess risk declines when exposure is removed. The greatest excess risk occurs 5-14 years after cessation of exposure, higher than in the 0-4 year category. The reason for this increase is unknown, but is likely the result of small

numbers, as a test of the hypothesis of homogeneity of the two estimates was nonsignificant ($P = 0.45$). After 5 years, the exposure risk gradient declines with years since cessation of exposure from a maximum of 12.3% 5-14 years after cessation to 0.7% after 25 or more years (Table 2). The radon effects decline to 0.7% per CWLM after 25 years since exposure stopped if arsenic exposure was ignored, or to zero if arsenic was included in the modeling. Any conclusion, however, that radon effects ultimately disappear 25 or more years after exposure is premature until there are further analyses of other data sets.

The BEIR IV risk model included radon effects which diminish with attained age (15). The β estimate was multiplied by 1.2 for age at risk less than 55 years, by 1.0 for ages 55-64, and by 0.4 for ages 65 and greater. The YTC data did not exhibit a significant decline in radon risk with age; however, a nonsignificant reduction was seen.

Animal studies have suggested that long duration of radon exposure at low intensity is more deleterious than short duration of exposure at high intensity (31, 32). This pattern has not been consistently observed in human data. Increasing risk with duration for fixed cumulative exposure has been reported among the Czech miners (6, 13). In the four cohorts which were part of the BEIR IV analysis, this risk pattern occurred in the Colorado Plateau uranium miners' cohort and, to a lesser extent, in the Canadian Beaverlodge cohort, but was not seen in the other cohorts and was not included in the modeling when all cohorts were combined (15). We found a strong effect of decreasing risk with increasing intensity when controlling for cumulative radon exposure. The risk dropped about 10-fold from the lowest to the highest category of radon exposure rate.

In previously reported studies, miners generally begin working in their mid-twenties. Thus, it has not previously been possible in cohorts of miners to evaluate the impact on lung cancer risk of radon exposures which occur in childhood. Morphological and physiological considerations have led some to suggest that radon exposure may have a greater effect among those exposed during childhood. Investigators point to results among Japanese atomic bomb survivors, *i.e.*, persons who were children at the time of the bombing have the greatest lung

cancer risk (33). In their recent report, the Radon Task Force of the International Commission on Radiological Protection assumed a constant (in time) excess relative risk model and ascribed an excess of 1% per CWLM for miners and 0.7% for domestic radon exposure. Based on the Japanese experience, the Task Force increased the lung cancer excess risk parameter by a factor of three for exposures under age 20 years to 3% per CWLM for miners and 2.1% for domestically exposed persons (22). It is, of course, conjectural whether the highly penetrating gamma and neutron irradiations, which were experienced by the Japanese, produce effects on lung tissue that are similar to low penetrating α -irradiation from the decay of inhaled radon and its progeny. As yet, studies among domestically exposed groups have been unable to develop a sufficiently detailed radon exposure history to address the effects of exposure in childhood.

The YTC data offered a unique opportunity to directly evaluate the effects of childhood exposure to radon. Among exposed workers, 36% of the cases and 38% of the controls were first exposed under the age of 13 years. We found no indication of a differential effect of radon exposure, as the increase in risk was similar regardless of age first exposed.

Several studies of the joint relationship of smoking and radon exposure have been reported (2, 7, 12, 13, 19, 34-40). However, formal analyses based on fitting statistical models have been carried out in only two populations (15, 16, 21). In the largest data set which is currently available, the additive model was statistically rejected, while the "best" model was intermediate between additive and multiplicative. The association of the smoking and radon, however, was consistent with a multiplicative relative risk model.

Our data were the second largest occupational case series to consider the joint association of tobacco use and radon exposure with lung cancer. Our results were consistent with a range of models from additive to submultiplicative and thus in general agreement with previous analyses that an intermediate model is the most likely.

The results of Tables 4 and 5 suggest that the declining gradient of exposure risk with years since cessation of exposure and with increasing exposure rate was unlikely to be due to patterns of tobacco consumption. The risk trends remained after adjustment for duration and cumulative waterpipe use. In addition, few workers quit smoking more than 1 year prior to diagnosis. In our group of subjects, 12 cases and seven controls, or 11%, had stopped smoking waterpipes. The crude odds ratios for current pipe smokers and ex-pipe smokers relative to non-pipe smokers were 2.8 and 4.1, respectively. The higher risk among exsmokers may be due to small numbers, or to cases stopping smoking due to prodromal symptoms; however, there were insufficient data on years since last use and reason for quitting for a definitive evaluation.

The primary method of tobacco consumption among workers was waterpipes. Although clearly deleterious, smoke from waterpipes may act differently from cigarette smoke, due to the smoke being drawn through a water bath, the generally unprocessed type of tobacco which is used and the different pattern of inhalation. Previous reports show that the patterns of lung cancer risk with tobacco use, although not necessarily the magnitudes of risk, are similar for dark and light cigarette smokers (41), pipe smokers, and cigar smokers (42). It is thus likely that waterpipe users also share similar risk patterns and therefore can help shed light on the joint association of tobacco use and radon exposure, although further work is needed to clarify this issue.

Eighteen workers smoked cigarettes exclusively, while only

four were nonsmokers. A reviewer suggested that the low relative risk for cigarette use (1.2, with 95% confidence interval 0.1-13.9) may indicate some misclassification of tobacco use. This issue is difficult to address, but the low relative risk is likely the result of nonintensive cigarette consumption habits. Cigarette-only smokers and mixed waterpipe and cigarette smokers consumed means of 12 and nine cigarettes per day with mean durations of 32 and 34 years, respectively. In addition, because of the high proportion of smokers, nonsmokers may be passively exposed to a high level of environmental tobacco smoke. Studies which are currently in the field should help address the issue.

Because cases represent prevalent disease, we restricted analyses to all cases and to the more recently diagnosed lung cancers. Analyses of all 107 cases who were diagnosed between 1971 and 1984 and were living at the time of interview were quite similar. Using all subjects, the excess was 1.7% per CWLM, which equals the 1.7% of Table 2. Restricting analysis to the 45 cases and 45 controls diagnosed in 1984, the excess was similar at 1.1%.

There is some evidence that oat cell tumors may be more closely linked to radon exposure than other cell types (15) and because of differential survival, a prevalent case series may potentially be biased. This appears unlikely in our case series. Of the 107 lung cancer cases from 1971, 60 were histologically classified, and of those 49 (82%) were squamous cell tumors. The preponderance of the squamous type appears unrelated to survival, as the prevalence was 78% for cases diagnosed and classified through 1980, 85% in 1981-1983 and 83% in 1984. It is likely that the large proportion of squamous cell tumors is due to the high prevalence of tobacco use and due to classifications being based primarily on sputum cytology.

In summary, results of this case control study show that the radon and lung cancer relationship is consistent with a linear relationship in cumulative exposure, but that the exposure response is not constant, declining with time since cessation of exposure and, possibly, with attained age. It also appears that for fixed cumulative exposure long duration of exposure at a low exposure rate may be more deleterious than short exposure at a high rate. Finally, our data agree with previous formal analyses of the joint effects of tobacco use and radon exposure. We found that the association of the two factors are likely best described by a model between additive and multiplicative.

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